

CLAIMS

We claim:

1. A method of antagonizing a naturally occurring TNFSF protein comprising contacting a naturally occurring TNFSF monomer protein with a variant TNFSF monomer protein comprising at least a variant extracellular domain of a TNFSF protein, to form a mixed TNFSF oligomer.
2. A method according to claim 1 wherein said mixed oligomers have reduced receptor signaling as compared to wild-type oligomers.
3. A method according to claim 2 wherein said mixed oligomers are substantially incapable of activating receptor signaling.
4. A method according to claim 1 wherein said mixed oligomer interacts with a receptor interface in at least one receptor binding site to render said receptor substantially incapable of activating receptor signaling.
5. A method according to claim 1 wherein said variant TNFSF monomer protein comprises at least one receptor contact domain that has reduced affinity for a desired receptor as compared to its corresponding wild-type TNFSF protein and retains the ability to interact with other TNFSF monomers.
6. A method according to claim 1, wherein said variant TNFSF monomer protein physically interacts with a naturally occurring TNFSF monomer protein to reduce the ability of the naturally occurring TNFSF to activate at least one receptor.
7. A method according to claim 1, wherein said variant TNFSF protein is a fusion protein.
8. A method according to claim 1 wherein said variant protein is chemically modified.
9. A method according to claim 8, wherein said chemical modification is PEGylation.
10. A method according to claim 8, wherein said mixed oligomer comprises covalent cross-linkages between monomers.
11. A method according to claim 10, wherein said mixed oligomer comprises at least one linker peptide between monomers.
12. A method according to claim 11, wherein said linker peptide is a sequence of at least one and not more than about 30 amino acid residues.

13. A method according to claim 12, wherein said linker peptide is a sequence of at least 5 and not more than about 20 amino acid residues.

14. A method according to claim 13, wherein said linker peptide is a sequence of at least 10 and not more than about 15 amino acid residues.

15. A method according to claim 11, wherein the linker peptide comprises at least one of the following amino acid residues: Gly, Ser, Ala, or Thr.

16. A method of making a mixed TNFSF oligomer comprising contacting at least one variant TNFSF protein comprising at least a variant extracellular domain of a TNFSF monomer protein with a homo-oligomer comprising naturally occurring TNFSF monomer proteins, under conditions whereby at least one naturally occurring TNFSF monomer exchanges with a variant monomer to form a mixed oligomer..

17. A mixed TNFSF oligomer comprising at least one variant TNFSF protein comprising at least a variant extracellular domain of a TNFSF monomer protein and a naturally occurring TNFSF monomer protein.

18. A variant TNFSF monomer protein comprising at least a variant extracellular domain of a TNFSF protein.

19. A variant TNFSF protein wherein said variant TNFSF protein will interact with a receptor interface in at least one receptor binding site to render said receptor substantially incapable of activating receptor signaling.

20. A variant TNFSF protein according to claim 18 comprising at least one receptor contact domain that has reduced affinity for a desired receptor as compared to its corresponding wild-type TNFSF protein and retains the ability to interact with other receptor interaction domains.

21. A mixed TNFSF oligomer comprising at least one variant TNFSF protein monomer according to claim 18, wherein said mixed oligomer has reduced ability to activate the corresponding receptor as compared to a wild-type oligomer.

22. A variant TNFSF protein according to claim 18, wherein said variant TNFSF protein physically interacts with a naturally occurring TNFSF protein to form mixed trimers.

23. A mixed TNFSF oligomer comprising at least one variant TNFSF protein monomer according to claim 18 comprising a modification at a receptor contact position.

24. A variant TNFSF monomer protein according to claim 18, wherein said variant TNFSF protein comprises a modification at a trimer interface position.

25. A variant TNFSF protein according to claim 18, wherein said variant TNFSF protein physically interacts with its corresponding naturally occurring TNFSF protein.

26. A variant TNFSF protein according to claim 18, wherein said variant TNFSF protein physically interacts with a non-corresponding naturally occurring TNFSF protein.

27. A recombinant nucleic acid encoding the variant TNFSF monomer protein of claims 18-26.

28. An expression vector comprising the recombinant nucleic acid of claim 27.

29. A host cell comprising the recombinant nucleic acid of claim 27.

30. A host cell comprising the expression vector of claim 28.

31. A method of producing a non-naturally occurring TNFSF protein comprising culturing the host cell of claim 29 or 30 under conditions suitable for expression of said nucleic acid.

32. A method according to claim 31, further comprising recovering said TNFSF protein.

33. A pharmaceutical composition comprising a variant TNFSF protein according to claims 18-26 and a pharmaceutically acceptable carrier.

34. A method for treating a TNFSF related disorder comprising administering a variant TNFSF protein of claim 18-26 to a patient in need of said treatment.

35. A method according to claim 34, wherein said TNFSF related disorder is an autoimmune disease.

36. A variant TNFSF protein according to claims 18, wherein at least one modification is non-conservative.

37. A variant TNFSF protein according to claims 18, wherein at least one modification is a surface modification.

38. A variant TNFSF protein according to claims 36, wherein said modification is located within a domain selected from the group consisting of: Large Domain, Small Domain, DE Loop, Trimer Interface and combinations thereof.

39. A variant TNFSF protein according to claim 38, wherein at least one of said Large Domain positions is selected from the group consisting of TNFA corresponding positions 28, 29, 30, 31, 32, 33, 34, 63, 64, 65, 66, 77, 68, 69, 112, 113, 114, 115, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146 and 147.

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40. A variant TNFSF protein according to claim 38, wherein at least one of said Small Domain positions is selected from the group consisting of TNFA corresponding positions 72, 73, 74, 75, 76, 78, 79, 95, 96, 97 and 98.

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41. A variant TNFSF protein according to claim 38, wherein at least one of said DE Loop positions is selected from the group consisting of TNFA corresponding positions 84, 85, 86, 87, 88 and 89.

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42. A variant TNFSF protein according to claim 38, wherein at least one of said Trimer interface positions is selected from the group consisting of TNFA corresponding positions 11, 13, 15, 34, 36, 53, 54, 55, 57, 59, 61, 63, 72, 73, 75, 77, 119, 87, 91, 92, 93, 94, 95, 96, 97, 98, 99, 102, 103, 104, 109, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 147, 148, 149, 151, 155, 156 and 157.

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43. A variant TNFSF protein according to claim 42, wherein at least one of said Trimer Interface positions is selected from the group consisting of: 57, 34, and 91.

44. A variant TNFSF protein according to claim 18, wherein said variant TNFSF protein antagonizes soluble naturally occurring TNFSF proteins.

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